Original Article

Demystifying the Relevance of Size Amongst Macro- and Micro-Corticotropinoma: Experience in 206 Patients

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Abstract

Objective: In individuals with adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome (CS), to estimate the differences between micro-corticotropinoma (size ≤6 mm and 6-10 mm), macro-corticotropinoma (>10 mm) and ectopic Cushing's syndrome (ECS), in relation to their epidemiological, clinical and biochemical parameters. **Methods:** In individuals with CS, the clinical and hormonal parameters, and magnetic resonance imaging of sella were collected from 1984 to 2019. A total of 138 cases of micro-corticotropinoma, 47 cases of macro-corticotropinoma and 21 cases of ECS were compared. **Results:** Except for size, there were no differences in biochemical and hormonal parameters of macro- and micro-corticotropinoma, irrespective of their size (≤6 mm, 6-10 mm and >10 mm). In comparison to Cushing's disease (CD), individuals with ECS had a male predominance (F:M ratio of 2.4:1 vs. 0.5:1), shorter duration from onset of symptoms to diagnosis (24 vs. 12 months). They also had a higher ACTH (139 vs. 65.8 pg/ml), 0800h cortisol (1200 vs. 880 nmol/l), 2300h cortisol (1100 vs. 700 nmol/l) and cortisol levels after high dose dexamethasone suppression test (1050 vs. 244.5 nmol/l). **Conclusion:** The biochemical phenotype of macro-corticotropinoma resembles that of micro-corticotropinoma despite their larger tumour size, suggesting that the former is relatively less functional. Micro-corticotropinoma ≤6 mm and 6-10 mm have a similar clinical and biochemical profile. As compare to CD, ECS is characterised by a higher disease burden as reflected in their higher cortisol, more autonomicity and loss of rhythmicity.

Keywords: Cushing's, ectopic, macro-corticotropinoma, micro-corticotropinoma

Introduction

Endogenous Cushing's syndrome (CS) is due to excess glucocorticoid production, which can be either adrenocorticotrophic hormone (ACTH) dependent or independent. ACTH dependent CS can further occur due to a pituitary microadenoma (adenoma size ≤10 mm), macroadenoma (adenoma size >10 mm) or an ectopic source of ACTH/CRH production.[1] While all of them are associated with an increase in ACTH secretion, there exist substantial differences as well as similarities amongst the three. Knowing about these is important to fully understand their biological nature and to assist in distinguishing corticotropinoma from ECS. Currently available literature comparing these three is scant and when available is primarily comparing ectopic Cushing's syndrome (ECS) and CD as a whole, that is, comprising both macro- and micro-corticotropinoma.[2,3] Also, the differences between micro- and macro-corticotropinoma have not been clearly defined.[4-6] The current study aims to compare micro-corticotropinoma, macro-corticotropinoma and ECS in terms of their epidemiological, clinical and biochemical parameters in individuals with ACTH-dependent CS.

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Material and Methods

This was a single centre study carried out in the Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, a referral centre for endocrine diseases, over a period of 35 years from 1984 till 2019. The data from year 2004 onwards was collected prospectively using

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a standard institution protocol and prior to the year 2004 was obtained retrospectively from medical records. The study was approved by the Institutional Ethics Committee (INT/IEC/85). As the manuscript does not contain any content which can reveal patient identity, written informed consent for publication of the clinical details was only obtained from the prospective participants.

The diagnosis of Cushing's syndrome was based on clinical features and further confirmed by investigations in accordance with Endocrine Society guidelines.[7] Baseline demographic data for this analysis included age, gender, duration of symptoms prior to diagnosis, body mass index, hypertension and diabetes mellitus. Hypertension was defined as resting blood pressure ≥140/90 mmHg or when the patient was already on anti-hypertensive treatment.[8] Diabetes was defined as per American Diabetes Association criteria or when the patient was already on anti-diabetic treatment.[9] ACTH dependency was confirmed by 0800h ACTH value of >20 pg/ml. The localisation of ACTH to pituitary or extra-pituitary site was done using Bilateral Inferior Petrosal Sinus Sampling (BIPSS), high dose dexamethasone suppression test (HDDST), Contrast Enhanced Magneticic Resonance Imaging (CEMRI) of sella, Contrast-Enhanced Computed Tomography (CECT) of chest and abdomen and ^{68}Ga DOTATE Positron Emission Computed Tomogrophy (PET-CT),[7].[10] The decision of performing these tests and imaging was decided on an individual basis by a team comprising of endocrinologist, neurosurgeons, radiologist and nuclear medicine physicians. HDDST was performed with per oral administration of 2 mg dexamethasone every six hourly for 48 hours. A suppression of cortisol by >50% after HDDST was considered as suppressible, while an increase of >8% from baseline (more than the coefficient of variation for cortisol assay), was considered as a "paradoxical rise".[11] For the current study, definitive diagnosis of CD was based on either demonstration of adenoma on histopathology or development of Nelson's syndrome for those undergoing total bilateral adrenalectomy. The diagnosis of Nelson syndrome was based on a newly appearing or expanding (>2 mm) pituitary adenoma with or without ACTH level rise.[12] Histopathological examination of the excised tissue was considered as gold standard for diagnosis of ECS.

Hormonal and biochemical analysis

Until 2009, plasma cortisol was measured by in-house radioimmunoassay (RIA) using tritium labeled cortisol after dextran charcoal separation with an intra- and inter-assay coefficients of variation being <8% and after that by electro-chemiluminescence-imm unoassay (ECLIA) (ELECSYS-2010, Roche Diagnostics, Germany). ACTH levels were measured by ECLIA (ELECSYS Roche Diagnostics, Germany) 2009 onwards with intra- and inter-assay CV of 1.4–2.8% and 2.3–6.4%, respectively, and prior to that by RIA (Biosure technologies, Nivellis, Belgium) with intra- and inter-assay CV of 4.7 to 8%.

Statistical analysis

Statistical analyses were performed using Statistical Package of Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY). Continuous variables were expressed as median plus inter-quartile range and discrete variables as proportions. Shapiro–Wilk's test was used for assessing normality and levene's test for inequality of variances. Mann–Whitney or Kruskal–Wallis was used to compare difference between means of variable with inequality of variance, as appropriate. Chi-square test or Fischer exact was used to examine difference between proportions. Correlation between two continuous variables was assessed using Spearman's rank correlation coefficient for nonparametric variables. Receiver operating curve (ROC) were constructed for estimating area under curve (AUC), keeping Cushing's disease or ectopic Cushing's as a state variable as appropriate. All comparisons were done at a level of significance of < 0.05.

Results

A total of 206 patients were diagnosed with ACTH dependent CS over 35 years, of which 138 had micro-corticotropinoma, 47 had macro-corticotropinoma and 21 had ECS. The median tumour diameter was 5 mm (IQR; 4 mm to 6.97 mm) for micro-corticotropinoma and 19 mm (IQR; 12 mm to 27 mm) in macro-corticotropinoma. The etiology of ECS was bronchial neuroendocrine neoplasm (NEN) (n = 7), thymic NEN (n = 7), medullary thyroid carcinoma (n = 2), pancreatic NEN (n = 2), paraganglioma (n = 1), colon NEN (n = 1) and hepatic NEN with unknown primary (n = 1).

Epidemiological and clinical profile

The epidemiological and clinical profile of patients with CD and ECS is shown in Table 1. The median age of presentation was 32 years in macro-corticotropinoma and ECS and 28 years in micro-corticotropinoma. As compared to CD, those with ECS had a male predominance (F: M ratio of 0.5:1 vs. 2.5:1; P = <0.001), shorter duration from onset of symptoms to diagnosis (lag time of 1 vs. 2 years; P = 0.002). As compared to corticotropinoma, individuals with ECS had higher percentage of individuals having discriminatory features in the form of easy bruisability, while discriminatory features affected those with micro- and macro-corticotropinoma equally [Table 1]. In addition to the aforementioned parameters, the presence of hypertension (71.9% vs. 78.8%, p: 0.551) and diabetes mellitus (54.1% vs. 60.9%, p: 0.483) was also similar between macro- and micro-corticotropinoma. Furthermore, visual field disturbances were present in 21.7% of the individuals with macro-corticotropinoma.

Comparison of biochemical and hormonal parameters in CD and ECS

The biochemical profile of patients with CD and ECS is shown in Table 1. As compared to CD, those with ECS had a higher serum 0800h and 2300h cortisol [1200 nmol/l vs. 857.6 nmol/l, P = 0.008 and 1100 nmol/l vs. 677.5 nmol/l, P = <0.001, respectively] and 0800h ACTH levels [139 pg/ml vs.

Table 1: Comparison of epidemiological, clinical and biochemical parameters in micro-corticotropinoma, macro-corticotropinoma and ectopic Cushing's syndrome (ECS)

	Micro-corticotropinoma (*n*=138)	Macro-corticotropinoma (*n*=47)	ECS (*n*=21)	*P* ECS Vs. Micro	*P* ECS Vs. Macro	*P* Micro Vs. Macro
Sex (F: M)	2.36:1	2.91:1	0.5:1	<0.01	<0.01	0.571
Age (years)	28	32	32	0.300	0.936	0.162
Median (IQR)	(20-36)	(20-42)	(22-35)			
Lag time*(years)	2	3	1	0.002	0.005	0.380
Median (IQR)	(1-4)	(1-5)	(0.5-2)			
BMI (kg/m^2)	26.9	28.1	27.9	0.796	0.491	0.422
Median (IQR)	(23.8-29.5)	(25.5-31.5)	(22.8-30.9)			
Discriminatory Features						
Stria	75.6%	65.2%	71.5%	0.698	0.655	0.105
Proximal Myopathy	85.3%	65.2%	85.7%	0.980	0.095	0.003
Easy Bruisability	58.5%	56.5%	95%	<0.001	0.001	0.881
0800h cortisol						
(nmol/l)	836.6	893.4	1200	0.006	0.101	0.474
Median (IQR)	(664.5-1100)	(660-1200)	(710.5-1530)			
2300h cortisol (nmol/l)	687.3	667,5	1100	0.001	0.003	0.756
Median (IQR)	(520.4-890)	(494.9-875.7)	(697-1457)			
0800 ACTH	64.67	70.3	139	<0.001	<0.009	0.144
(pg/ml)	(35.1-103.3)	(42.8-140.2)	(94-233)			
Cortisol post LDDST+ (nmol/l)	542.8	492	1092	0.001	0.003	0.756
Median/IQR	(267.4-777.5)	(262-798.1)	(609.3-1351)			
Cortisol post HDDST$ (nmol/l)	242.3	258.5	1050	<0.001	<0.001	0.978
Median/IQR	(101.6-555.1)	(76.8—623.6)	(656-1265)			
Post HDDST suppression>50%	70.5%	67.5%	11.1%	0.001	<0.001	0.722
% (*n*)	(93)	(27)	(2)			
HDDST suppression (%)	69.5	77.8	19.9	<0.001	<0.001	0.594
Median/IQR	(43.4-89.6)	(44.4-89.2)	(6.25-36.1)			
Paradoxical rise on HDDST	6.1%	0%	22.2%	0.018	_	_

*Statistical significance; +LDDST: Low dose dexamethasone suppression test; $: HDDST: High dose dexamethasone suppression test

63.8 pg/ml, *P* = <0.001]. Also, individuals with ECS had higher cortisol levels after low dose dexamethasone (LDDST) [1092 nmol/l vs. 510 nmol/l, *P* = <0.001] and HDDST [1050 nmol/l vs. 244.5 nmol/l, *P* = <0.001]. A paradoxical rise of cortisol after HDDST was seen in 22.2% (n = 4; two bronchial NEN and one pancreatic NEN and thymic NEN, each) of individuals with ECS. The biochemical comparison of patients with ECS showing paradoxical rise after HDDST vs. those without it is shown in Table 2. Those with paradoxical response on HDDST had a shorter lag time from onset of symptoms to diagnosis and a lower 0800h and 2300h cortisol despite having a similar ACTH value.

There were no significant biochemical and hormonal differences between patients of macro- and micro-corticotropinoma [Table 1]. Serum ACTH levels showed a significant positive correlation with tumour size overall (r = 0.222; *P* = 0.008) and for macro-corticotropinoma (r = 0.336; *P* = 0.034), while it showed a nonsignificant positive correlation in micro-corticotropinoma (r = 0.154; *P* = 0.124). In addition, as compared to macro-corticotropinoma, micro-corticotropinoma secreted more ACTH (4.54 pg/ml/mm vs 13.55 pg/ml/mm, *P* < 0.001) and cortisol (44.73 nmol/ml/mm vs 161.79 nmol/ml/mm, *P* < 0.001) per millimetre adenoma size [Figure 1]. A biochemical cure, defined as 0800h serum cortisol of <350 nmol/l or ONDST suppressible at three months after surgery, was seen in 73.7% and 56.5% of the individuals with micro- and macro-corticotropinoma, respectively (p = 0.083). A tumour residue on imaging at three months after surgery was seen in 28.9% and 56.5% individuals with micro- and macro-corticotropinoma, respectively (p = 0.027).

Table 2: Comparison of patients with ectopic Cushing's syndrome based on response on HDDST (*n*=18)

	Paradoxical rise (*n*=4)	No Paradoxical rise (*n*=14)	*P*
AGE (years)	27.5	31.5	0.101
Median/IQR	(22.5-47.5)	(19-34)	
Lag Time (months)	5	12	0.062
(range)	(3.5-15)	(12-24)	
0800 cortisol (nmol/l)	600	1390	0.019
Median/IQR*	(595-958)	(1148-2400)	
2300h cortisol (nmol/l)	663	1240	0.025
Median/IQR	(560-936)	(900-1500)	
0800H ACTH (pg/ml)	119	115	0.433
Median/IQR	(60.8-139)	(88-359)	

*IQR: Interquartile range

The comparison of biochemical and hormonal characteristics between micro-corticotropinoma of size ≤ 6 mm, >6 mm and ectopic Cushing's syndrome is shown in Table 3. The age, lag time, 0800h and 2300h cortisol, 0800h ACTH and cortisol levels after LDDST and HDDST were similar in the two subgroups of micro-corticotropinoma (≤6 mm and 6-10 mm). However, both size subgroups as compared to ECS had a lower ACTH, 0800h and 2300h cortisol and post LDDST and HDDST cortisol levels. There was no difference in postsurgical biochemical cure (75.4% vs. 72.4%, $P = 0.760$) and anatomical residue (30.0% vs. 28.6%, $P = 0.923$) at three months between micro-corticotropinoma of size ≤6 mm and >6 mm.

The findings from ROC analysis for differentiating micro-corticotropinoma and ECS are shown Table 4. The maximum area under the curve of 0.844 (0.773–0.914) was seen with HDDST, with >50% suppression of cortisol from baseline having a sensitivity and specificity of 69.8% and 88.9%, respectively. A specificity of more than 90%, which is more relevant clinically, was seen at a suppression of cortisol from baseline by >60% after HDDST. A suppression of cortisol by >41% from baseline after LDDST predicted a suppression of greater than 50% on HDDST with sensitivity and specificity of 60.3% and 84.1%, respectively. For distinguishing between ECS and micro-corticotropinoma the optimal cut-off for ACTH was 96 pg/ml with a sensitivity and specificity of 77.8% and 70.3%, respectively. An ACTH value of >90 pg/ml yielded a sensitivity and specificity of 77.8% and 67.1%, respectively while a specificity of more than 90% for diagnosis of ECS was seen at a cut-off of 177 pg/ml.

Discussion

The current study has compared the clinical and hormonal features of the three main etiologies of ACTH dependent CS in relation to their size (macro-corticotropinoma vs. micro-corticotropinoma and micro-corticotropinoma ≤6 mm vs. 6–10 mm in size) and site (ECS vs. CD). Within the corticotropinoma subgroups based on size (macro-corticotropinoma vs. micro-corticotropinoma and micro-corticotropinoma ≤6 mm and 6–10 mm in size), all had a similar clinical and biochemical profile. As compared to CD, individuals having ECS have a higher disease burden

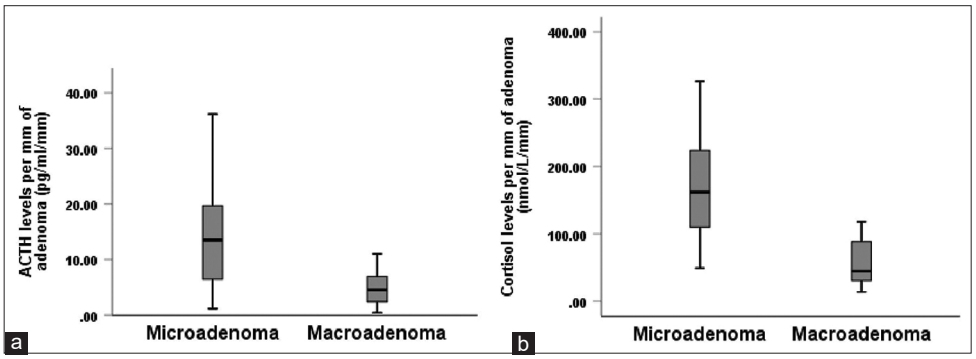

Figure 1: Box-Plot graph demonstrating, (a) serum levels of ACTH per millimetre of maximum adenoma size and (b) serum cortisol levels per millimetre of maximum adenoma size

Table 3: Comparison of biochemical parameters between micro-corticotropinoma of size≤6 mm, >6 mm and Ectopic Cushing's syndrome (ECS)

	Micro- Corticotropinoma ≤6 mm *n*=79	Micro- Corticotropinoma >6 mm *n*=33	ECS *n*=21	*P* ≤6 mm Vs. >6 mm	*P* ≤6 mm Vs. ECS	*P*>6 mm Vs. ECS
Age (years)	26	30	32	0.432	0.240	0.450
Median/IQR	(19.3-35)	(21.5-36.5)	(22-35.5)			
Lag time (years)	2	2	1			
(range)	(1-4)	(1.2-5)	(0.6-2)	0.677	0.004	0.007
0800h Cortisol (nmol/l)	865	880	1200	0.846	0.006	0.027
Median/IQR	(576.1-1068)	(686.5-1056.5)	(710.5-1530)			
2300h Cortisol (nmol/l)	683	714	1100	0.647	0.001	0.008
Median/IQR	(509.5-915)	(530-871.5)	(697-1457)			
0800hACTH (pg/ml)	59.5	71.1	139	0.319	<0.001	<0.006
Median/IQR	(36.7-95.5)	(39.1-128.8)	(94-233)			
Cortisol post LDDST (nmol/l)	410	555.8	1092	0.633	<0.001	0.002
Median/IQR	(231.8-905.8)	(284.8-747.3)	(609.3-1351)			
Cortisol post HDDST (nmol/l)	207.7	286.9	1050	0.623	<0.001	<0.001
Median/IQR	(72.8-580.8)	(120-558.3)	(656-1265)			
% Suppression on HDDST	70.9	68.2	19.9	0.674	<0.001	<0.001
Median/IQR	(43.4-90.8)	(49.4-87.5)	(6.2-36.2)			

Table 4: Optimal cut-off for various biochemical parameters in distinguishing Cushing's disease and ectopic Cushing's disease

	Percentage suppression of cortisol on LDDST from baseline*	Percentage suppression of cortisol on HDDST from baseline*	0800h cortisol (nmol/l)#	2300h Cortisol (nmol/l)#	0800h ACTH (pg/ml)#
AUC	0.686	0.844	0.671	0.731	0.776
P	(0.587-0.785)	(0.773-0.914)	(0.529-0.813)	(0.605-0.856)	(0.667-0.885)
	0.005	<0.001	0.010	0.001	<0.001
Optimal cut-off	>27%	>40%	>1044	>873	>96
	Sens: 64.2%	Sens: 80%	Sens: 61.9%	Sens: 66.7%	Sens: 77.8%
	Spec: 71.4%	Spec: 83.3%	Spec: 71.4%	Spec: 74%	Spec: 70.3%
Cut-off with >90% specificity	>48%	>60%	>1320	>1193	>177

*State variable was taken as Cushing's disease due to microadenoma; # state variable was taken as ectopic Cushing's syndrome. LDDST: Low dose dexamethasone suppression test; HDDST: High dose dexamethasone suppression test. Sens: sensitivity, Spec: specificity

as suggested by their shorter duration from symptom onset to diagnosis, higher ACTH, 0800h and 2300h cortisol levels and a higher cortisol after LDDST and HDDST.

ECS, macro- and micro-corticotropinoma share a common feature of excess and autonomous ACTH production leading to a state of endogenous hypercortisolism. However, they have some differences which are well-described between ECS and CD but not within corticotropinoma i.e., macro-corticotropinoma vs. micro-corticotropinoma and micro-corticotropinoma of ≤ 6 mm and 6–10 mm. In this regard, the current study did not find any difference between biochemical and hormonal parameters in patients with macro- and micro-corticotropinoma. For macro-corticotropinoma to have a biochemical phenotype that is similar to micro-corticotropinoma, despite having a larger size suggest that they are less functional relative to their size. The same has been suggested earlier by Kakade H R *et al*., who have demonstrated a negative correlation between tumour size and functionality as adjudged by cortisol and ACTH secretion per mm of tumour size.[13] However, the findings suggesting reduced functionality of macro-corticotropinoma needs to corroborated further with a comprehensive evaluation of tumour functionality, which included but is not limited to measurement of precursor molecules and in-vitro tissue analysis. Furthermore, size plays an important role in further evaluation of micro-corticotropinoma. Since the original study by Hall *et al*. which showed a maximum pituitary incidentaloma of size 6 mm, multiple guidelines have used this cut-off to justify a differential approach for further evaluation in a case of suspected ACTH-dependent CS.[14,15] In situations with a microadenoma of >6 mm, one need corroborating non-invasive dynamic tests to prove it to be a corticotropinoma, while with microadenoma ≤6 mm one requires BIPSS to show pituitary as the source of excess ACTH.[16] In this regard, we did not find any difference in terms of severity, autonomicity or rhythmicity between micro-corticotropinoma of size ≤6 mm and >6 mm. Hence, the noninvasive dynamic testing which is based on tumour autonomicity is likely to hold a similar role in evaluation of micro-corticotropinoma, irrespective of their size. In addition, this size base differential approach needs to be reviewed for the following reasons. For any diagnostic procedure, the probability of having a disease after an investigation (i.e., post-test probability) is dependent on probability of disease prior to it (i.e., pre-test probability). In a patient with ACTH dependent CS, the pretest probability (i.e., prior to doing an MRI sella) of CD is between 80 and 90% and as such any pituitary adenoma identified on MRI has a very high probability of being a corticotropinoma, irrespective of its size. Also, extrapolating the maximum size of an incidentaloma to a case of suspected Cushing's syndrome may be inappropriate as autopsy studies have found pituitary incidentaloma larger than this, including macroadenomas. Hence in the setting of ACTH dependent hypercortisolism, the probability of an adenoma of size ≤6 mm being an incidentaloma is quite low to justify a differential approach to their diagnosis. Overall, the current study suggests that except for the tumour size, macro- and micro-corticotropinoma have a similar clinical and hormonal profile.

ECS are generally considered to be more severe and aggressive as compared to CD and a similar result was seen in the current study as well. Amongst the clinical parameters, ECS was male predominant and had a shorter lag time to presentation as compared to CS. Furthermore, in comparison to CD, ECS had a higher ACTH and 0800h cortisol levels suggesting a more severe disease, had a higher cortisol value after LDDST and lesser proportion of individuals showing suppression of > 50% on HDDST suggesting more autonomous ACTH production and lastly, a higher 2300h cortisol levels suggesting a more severe loss of rhythmicity. All these findings conform to what has been reported earlier.

Interestingly, 22% patients in ECS group instead of suppression depicted a paradoxical rise in cortisol after HDDST. This might be due to due to a completely erratic secretion of ACTH from these tumours which is not responsive to exogenous steroid or to the presence of aberrant glucocorticoid receptors on these tumours leading to an increase in ACTH secretion in response to dexamethasone administration. However, this needs to be explored further at molecular level. Additionally, we found that individuals with ECS showing paradoxical rise of cortisol on HDDST as compared to those showing any level of suppression had lower cortisol levels despite a

similar ACTH concentration. The exact mechanism behind such a finding remains elusive; however, it may suggest that the ACTH secreted by these tumours is immunoreactive but bioinactive or could reflect increased circulating POMC detected by ACTH immunoassays. Both of these scenarios in turn reflect the dedifferentiated state of the underlying tumour. Overall, these findings suggest that the tumours responsible for causing ECS behave quiet differently from either micro- or macro-corticotropinoma.

One of the important challenges in individuals with ACTH-dependent CS is to distinguish between ECS and micro-corticotropinoma. Amongst the various hormonal parameters evaluated in the current study, HDDST had the highest specificity of 83.3% at a cut-off of >40% suppression of 0800h cortisol from baseline. A similar result has been reported from other studies as well.[11,17] Another commonly used parameter for differentiating ECS and micro-corticotropinoma is an ACTH value of >90 pg/ml favouring ECS.[18] In our study at this cut-off, we found a sensitivity and specificity of 77.8% and 67.1%, respectively, suggesting that a substantial number of cases of micro-corticotropinoma may have ACTH value more than 90 pg/ml. To attain a specificity of more than 90%, a cut-off of 177 pg/ml was derived from the current study. Overall, we did not find any parameter to have a specificity exceeding the pre-test probability of CD, that is, more than 90%, at their optimal cut-off.

Conclusion

Amongst the three causes of ACTH-dependent CS (i.e., ECS, macro- and micro-corticotropinoma), ECS behaves differently from rest of the two and is characterized by higher disease burden as reflected by higher cortisol, more autonomicity and loss of rhythmicity. The biochemical phenotype of macro-corticotropinoma resembles that of micro-corticotropinoma despite their larger tumour size, suggesting that they are relatively less functional. Micro-corticotropinoma ≤6 mm and >6 mm have a similar clinical and biochemical profile.

Strength and Limitations

The current study has compared ECS, macro- and micro-corticotropinoma separately. The comparison of biochemical and hormonal characteristics of micro-corticotropinoma >6 mm and ≤6 mm further adds to the study strength. However, the limitations of the current study are-1) small number of patients with ectopic Cushing's syndrome; 2) non-availability of 24 hours urinary free cortisol, CRH and/or desmopressin stimulation test and 3) the retrospective data collection prior to the year 2004.

Statements and Declarations

Author's contribution

RW conceived the idea. RG, NJ, RW were involved in data extraction, analysis, manuscript writing and editing. SKB and AB assisted in data interpretation, manuscript preparation and editing.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and approval was granted by the Ethics Committee of Post Graduate Institute of Medical Education and Research, Chandigarh (INT/IEC/85).

Consent to participate

As the manuscript does not contain any content which can reveal patient identity, written informed consent for publication of the clinical details was only obtained from the prospective participants.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

ACTH: Adrenocorticotrophic hormone; CS: Cushing's Syndrome; ECS: Ectopic Cushing's Syndrome; CD: Cushing's Disease,; ONDST: overnight dexamethasone suppression test; LDDST: low dose dexamethasone suppression test; BIPSS: Bilateral inferior petrosal sinus sampling; HDDST: high dose dexamethasone suppression test; CEMRI: Contrast Enhanced Magnetic Resonance Imaging, CECT: Contrast-enhanced computed tomography; PET-CT: Positron Emission Computed Tomography; HPE: histopathological examination; RIA: radioimmunoassay; ECLIA: electro-chemiluminescence-immunoassay; NEN: neuroendocrine tumour.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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